JOURNAL OF HEPATOLOGY

A response-guided approach based on HBsAg kinetics may identify patients with the greatest chance of success

To the Editor:

We read with interest the paper by Ning *et al.* entitled "Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: A randomised open-label trial (OSST trial)" in the latest issue of the *Journal of Hepatology* [1]. The authors conducted a randomized open study (randomization: 1:1; peginterferon alfa-2a 180 μg/week or entecavir [ETV] 0.5 mg/day for 48 weeks) in HBe antigen (HBeAg)-positive CHB patients who had received ETV for 9–36 months, with HBeAg <100 PEIU/ml and HBV DNA ⩽1000 copies/ml. The primary end point was HBeAg seroconversion at week 48.

Their findings have practical implications on patients receiving long-term ETV therapy, because they demonstrate that it is possible to enhance the chances of HBeAg seroconversion and HBsAg loss by switching to a finite course of PegIFN alfa-2a therapy. Patients who lose HBeAg and have HBsAg levels <1500 IU/ml with ETV are recommended to switch to PegIFN because they have a good chance of HBsAg loss (22.2%) and HBeAg seroconversion (33.3%). Those, who still have HBsAg levels >1500 IU/ml at week 12 after switching, have a low chance of success (negative predictive value 98% for HBsAg loss and 95% for HBeAg seroconversion). These patients should consider stopping PegIFN.

In order to find an alternative solution to indefinite nucleos(t)ide analogue (NA) therapy, two concepts were developed: switching or add-on PegIFN alfa-2a. Both significantly increased the rate of HBeAg seroconversion and HBsAg loss. Recently, Brouwer *et al.* demonstrated that adding PegIFN to ETV increases the response rates in HbeAg-positive chronic hepatitis B patients [2].

A third approach was reported, which suggests that an extension of 48- to 96-week of PegIFN treatment may improve the chances of definite treatment in HBeAg negative chronic hepatitis B patients treated with NA [3].

We used this third strategy by extending PegIFN up to 96 weeks, which according to the evolution of the HBsAg titre provided a loss of HBsAg in six out of 10 patients with HBs seroconversion in two patients, regardless of the HBV genotype or *IL28B* status. The HBsAg titre decline constituted a useful tool to predict the loss of HBsAg and to determine the optimal duration of PegIFN add-on therapy. This concept of time-individualized therapy, based on HBsAg monitoring, was recently demonstrated with success in the IFN treatment of chronic hepatitis delta patients [4,5].

In conclusion, based on the Ning *et al.* study, in our hands and others, in order to increase the HBsAg clearance rate, we emphasize the benefits of both the switch to or add-on therapy and HBsAg monitoring to individualize the treatment and to implement stopping rules for ending or extending IFN treatment.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Ning Q, Han M, Sun Y, Jiang J, Tan D, Hou J, et al. Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: A randomised open-label trial (OSST trial). J Hepatol 2014;61:777–784.

[2] Brouwer WP, Xie Q, Sonneveld MJ, Zhang NP, Zhang Q, Tabak F, et al. Adding peginterferon to entecavir increases response rates in HBeAg-positive chronic hepatitis B patients: Week 96 results of a global multicenter randomised trial (ARES Study). J Hepatol 2014;60:S2.

[3] Lampertico P, Vigano M, Di Costanzo GG, Sagnelli E, Fasano M, Di Marco V, et al. Randomised study comparing 48 and 96 weeks peginterferon alpha-2a therapy in genotype D HBeAg-negative chronic hepatitis B. Gut 2012;62:290–298.

[4] Ouzan D, Penaranda G, Joly H, Halfon P. Optimized HBsAg titer monitoring improves interferon therapy in patients with chronic hepatitis delta. J Hepatol 2013;58:1258–1259.

[5] Ouzan D, Penaranda G, Joly H, Khiri H, Pironti A, Halfon P. Add-on peg-interferon leads to loss of HBsAg in patients with HBeAg-negative chronic hepatitis and HBV DNA fully suppressed by long-term nucleotide analogs. J Clin Virol 2013;58:713–717.

Philippe Halfon[1,*]
Guillaume Pénaranda[1]
Denis Ouzan[2]
[1]*Hôpital Européen, Laboratoire Alphabio, Marseille, France*
[2]*Institut Arnault Tzanck, Saint Laurent du Var, France*
*Corresponding author. Address: Hôpital Européen, Laboratoire Alphabio, 1 rue Melchior Guinot, 13003 Marseille, France.
Tel.: +33 4 13 42 81 00; fax: +33 4 91 79 20 44.
E-mail address: philippe.halfon@alphabio.fr